

## REMARKS

### The Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 10-12, 14, 16, 17, 19-21, 30, and 31 and have canceled claims 13, 15, and 18. Claims 2, 4-9, and 22-29 were previously canceled. Specifically, claim 1 has been amended to recite a chemically synthesized double stranded short interfering nucleic acid (siRNA) molecule wherein one or more pyrimidine nucleotides present one or both strands of said double stranded nucleic acid (siRNA) molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. Support for the amendment to claim 1 can be found, *inter alia*, in claims 13, 15 and 18 as originally filed, and at page 20, lines 10-20; page 43 line 9 to page 45 line 23; Figures 4 and 5; and SEQ ID NOS 579-626 and 643-650. Claim 1 and dependent claims 3, 10-12, 14, 16-17, 19-21, and 30-31 have been amended to recite the term “siRNA” rather than “siNA”. Support for these amendments can be found, *inter alia*, at page 2, line 12; page 8, line 2; page 74, lines 10 to 28, and throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

### Priority

The Office Action alleged that the instant application was not entitled to priority under U.S. Provisional Applications 60/363,124 filed on March 11, 2002 because “[t]here are no documents that arose from 60/363,124 for which priority is being claimed that recite siNA molecules specific to the instantly claimed target, CHRM3. The intervening references do not recite the instant target and therefore the instant application does not receive benefit of 60/363,124” (see Office Action at page 3). The Applicant respectfully disagrees with the Office’s assessment of the priority claim in view of the fact that the instant application claims

priority to PCT/US03/05028, filed on February 20, 2003, published as WO 03/74654. WO 03/74654, which was filed within one year of the 60/363,124 application, discloses the instantly claimed target, CHRM3, for example, at page 546 (entry for NM\_000740, Homo sapiens cholinergic receptor, muscarinic 3 (CHRM3) mRNA). Because PCT/US03/05028 was filed within one year of 60/363,124, because both PCT/US03/05028 and 60/363,124 recite the instantly claimed invention, and because the instant application is a continuation-in-part of PCT/US03/05028 and incorporates PCT/US03/05028 in its entirety, the instant invention is entitled to a priority date of at least March 11, 2002, the filing date of the 60/363,124 application.

As described in the previous response, filed on November 8, 2005, the present application claims priority to, *inter alia*, 60/363,124 (the '124 application), filed March 11, 2002. The claims presented above all find support in, *inter alia*, the '124 application. In particular, amended claim 1 finds support for chemically synthesized double stranded siRNA at p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the sense and antisense strands at p. 12, lines 4-7, p. 19, lines 11-14, p. 20, lines 16-20, p. 21, lines 3-6, and p. 25, lines 17-29; the antisense strand having between 18-27 nucleotides complementary to CHRM3 RNA at p. 18, lines 1-5, p. 12, line 6, p. 421, entry in Table III for GenBank Accession No. NM\_000740; and 2'-deoxy-2'-fluoro pyrimidine modifications at p. 6, line 19 to page 7, line 18 (where R3 of Formula II is F); page 10, lines 11-16 and 25-30; and page 11, lines 6-11 and 20-25.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
3	One or more ribonucleotides: p. 15, lines 3-9
10	Sense strand connected to antisense strand via linker molecule: p. 19, lines 20-21, 25, 28, p. 20 line 15, p. 38 lines 17-29
11	Polynucleotide linker: p 12, lines 13-26, p. 38, lines 18-29
12	Non-nucleotide linker: p 12, lines 13-26
14	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18

Claim	Support
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
19	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 14-15
20	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
21	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25
30	Terminal phosphate group: p. 8, line 26 to p. 9, line 13
31	Composition comprising the double stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

In view of these remarks, Applicant respectfully requests reconsideration of the priority claim.

**Rejection of Claims Under 35 U.S.C. § 103(a)**

Claims 1, 3, 10-21, 30 and 31 stand rejected as allegedly obvious over Elbashir *et al.*, 2001, *EMBO J.*, 20:6877-6888, in view of Forsythe *et al.*, 2002, *A. J. Respir. Cell Mol. Biol.*, 26:298-305, Sato *et al.*, 1999, *Neuroscience Letters*, 266:17-20, Tuschl *et al.* (WO 02/44321), Matulic Adamic *et al.* (U.S. 5,998,203) and Morrissey *et al.* (U.S. Publ. No. 2003/0206887). Claims 13, 15, and 18 have been canceled, rendering the rejection moot as to these claims. Applicants respectfully traverse the rejections as it applies to claims 1, 3, 10, 11-12, 14, 16-17, 19-21, 30 and 31.

Morrissey is not proper 102(e) prior art for the purposes of 35 U.S.C. § 103(a) because U.S. Publ. No. 2003/0206887 and the instant invention were, at the time the invention was made, subject to an obligation of assignment to the same entity, Sirna Therapeutics Inc. See MPEP § 706.02(l)(1).

Aside from the Morrissey reference, Applicants further submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. See MPEP §2143. Applicant submits that none of the cited

references, alone or in combination, teach or suggest an siRNA of about 18-27 nucleotides having the recited characteristics, and, in particular, having one or more pyrimidine nucleotides modified to 2'-deoxy-2'-fluoro pyrimidine nucleotides.

In the interest of advancing prosecution, claim 1 has been amended during prosecution and currently recites a chemically synthesized double stranded short interfering nucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein: each strand of said double stranded nucleic acid (siRNA) molecule is about 18 to about 27 nucleotides in length; the antisense strand of said double stranded nucleic acid (siRNA) molecule comprises nucleotide sequence that is complementary to a cholinergic receptor muscarinic 3 (CHRM3) nucleotide sequence comprising SEQ ID NO: 305; and the sense strand is complementary to the antisense strand; and one or more pyrimidine nucleotides present in one or both strands of said double stranded nucleic acid (siRNA) molecule comprises at least one chemically modified nucleotide in said sense strand and said antisense strand of said double stranded nucleic acid molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. These claim amendments further distance the Applicant's invention from any *prima facie* case of obviousness.

Contrary to the Office's allegation, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the cited references or to combine the teachings of the multiple reference to arrive at the presently siRNA molecules. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." See, *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for

piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). “Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.” *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000) (“particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed”).

As set forth in the previous response, Forsythe *et al.* merely teach the cDNA encoding the human m3 muscarinic receptor gene. Sato *et al.* teach that muscarinic receptor subtype m3 is present on various blood cells, including peripheral lymphocytes, and that muscarinic receptor *agonists* modulate the functions of lymphocytes. Because Sato *et al.* teaches that muscarinic receptor *agonists* modulate the functions of lymphocytes, the teachings of Sato *et al.* do not provide any motivation or suggestion to down regulate muscarinic receptor gene expression (as in the case of *antagonists*), let alone suggest the use of siRNA molecules targeting CHRM3 RNA comprising SEQ ID NO: 305. Therefore, the present invention, even without any reference to chemical modifications, would not be considered obvious in view of the prior art.

Elbashir (*EMBO J*, 2001) describes chemically synthesized siRNA duplexes with overhanging 3'-ends that mediate RNAi in *Drosophila* embryonic lysate. Tuschl teaches nothing more than what is described in Elbashir (the authors of Elbashir are co-inventors on Tuschl). Elbashir does not teach or suggest CHRM3 as a target for RNA interference using short interfering nucleic acids, let alone a siRNA molecule as presently claimed, i.e., siRNA selectively having pyrimidine nucleotides substituted with 2'-deoxy-2'-fluoro modifications. Matulic-Adamic teaches the use of 5' and 3' caps to prevent nuclease degradation of nucleic acid molecules. None of these cited references either individually or in combination render obvious the claimed invention. Importantly, the combination of references do not teach all of the limitations of the presently claimed invention. This alone is sufficient to obviate the rejection.

Further, one of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Elbashir (*EMBO J*, 2001) and Tuschl are the only references cited that teach a structure of the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. The teachings of Sato *et al.* do not even contemplate nucleic acid technologies and therefore there is nothing even remotely linking Sato and Forsythe to Elbashir and Tuschl. Furthermore, the nucleic acid technologies available in 1999, at the time Sato *et al.* was published, were essentially limited to antisense and ribozyme technology, as siRNA technology was not yet known. Although antisense and ribozymes are nucleic acid based technologies, they differ substantially from the present invention, both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs described by Elbashir (*EMBO J*, 2001).

The Office Action states that Elbashir and Tuschl are relied upon for teachings of RNAi and common modifications to siRNA duplexes. However, none of the cited references, alone or in combination, teach or suggest chemical modification of the siRNA duplex as is presently claimed, *i.e.*, where one or more pyrimidine nucleotides present one or both strands of the siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. Whereas the prior art may have taught the use of 2'-deoxy-2'-fluoro modifications in general as applied to long double stranded RNA, antisense or ribozyme molecules, the prior art does not teach or suggest the use of select modification of pyrimidine nucleotides with 2'-deoxy-2'-fluoro nucleotides, let alone such use in siRNA molecules targeting CHRM3.

In fact, the state of the art at the time of the instant invention taught away from such modifications. Thus, in this case, the knowledge of one of ordinary skill in the art at the time of filing prevented the inventive siRNA molecules claimed in the instant application from being realized by others. Elbashir and Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or

were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of pages 6881 and 6882 of Elbashir (also in Tuschl, page 46) describes 2'-deoxy and 2'-O-methyl modified siRNA duplexes and is reproduced below:

To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir (same as Figure 14 in Tuschl) clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where 2'-O-methyl substitutions were used, this modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbashir (Tuschl Pages 49-50),

2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Based on the teachings of "[t]he siRNA Users Guide" from Elbashir and Tuschl, for example, one of skill in the art would not have been motivated to make any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not have been motivated to pursue the presently claimed invention. This is evident from the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Elbashir and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (see, e.g., Bitko *et al.*, 2001, *BMC Microbiology*, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, *Malaria Journal*, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; Holen *et al.*, 2002, *Nucleic Acids Research*, 30, 1757-1766, Figures 1, 2 and 6). These

prior art references represent the state of the art at the time of filing and demonstrate that Elbashir and Tuschl taught away from the presently claimed invention.

Further, a plain reading of Elbashir teaches that modifications besides 3'-terminal deoxy nucleotides are not tolerated and likely interfere with protein association in siRNP assembly. As such, neither Elbashir nor Tuschl would have provided any motivation to a person skilled in the art to take the teachings of the prior art, e.g., antisense or ribozymes, and apply it to double stranded RNA molecules as presently claimed because Elbashir and Tuschl tried this approach and failed; Elbashir and Tuschl therefore teach away from using modifications beyond use of 2'-deoxynucleotides at the 3'-terminal positions of the double stranded RNA molecules. Thus, one of skill in the art would not have been motivated to selectively incorporate one or more 2'-deoxy-2'-fluoro modifications at pyrimidine positions within the double stranded RNA molecules as presently claimed.

A review of the state of the art clearly indicates that the applicants are the first to show that selective incorporation of 2'-deoxy-2'-fluoro modifications at pyrimidine positions are well tolerated in double stranded nucleic acid molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully down regulate gene expression. For example, in co-pending application USSN 10/444,853, published as US-2004-0192626, applicant has designed, synthesized, and tested several 2'-deoxy-2'-fluoro pyrimidine modified double stranded nucleic acid molecules having potent activity directed against several different gene targets (see for example Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-15). In contrast to the published reports of others at the time of filing, these co-pending applications demonstrate that application of 2'-deoxy-2'-fluoro pyrimidine modifications to double stranded nucleic acid structures are well tolerated for maintaining potent RNAi activity against CHRM3 and other target nucleic acid sequences.

For all of the reasons stated above, a person skilled in the art would not have been motivated to follow the teachings of Elbashir, or Tuschl, let alone the antisense or ribozyme art,

to make and use the double stranded nucleic acid molecules of the present invention to target human CHRM3 gene expression.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000). Applicant submits that no *prima facie* case of obviousness exists because, as described above, there would have been no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach against the instant claims. Because no *prima facie* case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims. Clarification of the claims by virtue of the present amendments further obviates the rejection.

For the reasons set forth above, Elbashir *et al.*, 2001, *EMBO J.*, 20:6877-6888, in view of Forsythe *et al.*, 2002, *A. J. Respir. Cell Mol. Biol.*, 26:298-305, Sato *et al.*, 1999, *Neuroscience Letters*, 266:17-20, Tuschl *et al.* (WO 02/44321), Matulic Adamic *et al.* (U.S. 5,998,203) and Morrissey *et al.* (U.S. Publ. No. 2003/0206887) do not teach or suggest making a chemically synthesized double stranded short interfering nucleic acid (siRNA) molecule comprising a sense strand and an antisense strand, wherein: each strand of said double stranded nucleic acid (siRNA) molecule is about 18 to about 27 nucleotides in length; the antisense strand of said double stranded nucleic acid (siRNA) molecule comprises nucleotide sequence that is complementary to a cholinergic receptor muscarinic 3 (CHRM3) nucleotide sequence comprising SEQ ID NO: 305; and the sense strand is complementary to the antisense strand; and one or more pyrimidine nucleotides present one or both strands of said double stranded nucleic

acid (siRNA) molecule comprises at least one chemically modified nucleotide in said sense strand and said antisense strand of said double stranded nucleic acid molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide with a reasonable expectation of success.

Therefore, because there would have been no motivation to combine the cited references, because there would have been no reasonable expectation of success in such a combination, and because the cited references in combination do not even teach the presently claimed invention, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

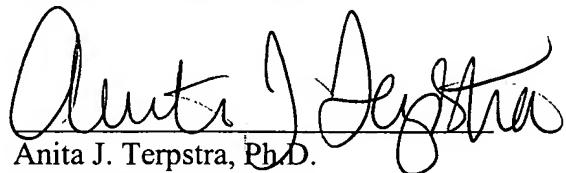
### **Obviousness-Type Double Patenting Rejections**

Claims 1, 3, 10-21, 30 and 31 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over the claims of copending application 10/919,866 for the reasons of record set forth in the office action mailed on 8/8/2005. Claims 13, 15, and 18 have been canceled, rendering the rejection moot as to those claims. With respect to claims 1, 3, 10-12, 14, 16-17, 19-21, 30, and 31, Applicant reiterates its request to defer addressing this rejection until the claims are otherwise in condition for allowance.

## Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below

Respectfully submitted,



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